MEMORANDUM

3 September 2003

To: File **P910001/S022/A001,A002,A003,A004**

From: John P. Holden, Ph.D.
FDA/CDRH/ODE/DCD/PVDB

Device: **CVX-300 Excimer Laser System**

Sponsor: Spectranetics Corporation
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Colorado Springs, CO 80907-5186

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This report includes an FDA summary of the clinical, statistical, and preclinical testing review memorandums regarding P910001/S022. This PMA Supplement from Spectranetics seeks marketing approval for the CVX-300 Excimer Laser System and 15 models of laser catheters for the treatment of critical limb ischemia (CLI). Ten of the catheter models have been previously approved for use in coronary arteries; five are new catheter models specific to this use in peripheral arteries to treat CLI.

Indications for Use:

The currently proposed indications for use are as follows: "For facilitating limb salvage in patients with critical limb ischemia (associated with Rutherford Categories 4, 5 and 6) who have angiographically evident culprit stenoses and/or occlusions in the SFA, popliteal and/or infrapopliteal arteries, who are poor surgical candidates and who are acceptable candidates for revascularization."

Review team

The FDA review team for this file is as follows:

Lead	John Holden, Ph.D.
Lead Clinical	Wolf Sapirstein, M.D.
Statistical	Barbara Krasnicka, Ph.D.
	Murty Ponnapalli, Ph.D.
Laser device:	Richard Felten
Biocompatibility, Packaging and Sterilization	Lisa Kennell
Bioresearch Monitoring	D. Laurie Bernato

The Office of Compliance determined that there is no need for an inspection for compliance with the Quality System (QS)/GMP regulations to cover PMA supplement P910001/S22. There are no technological changes not previously covered during previous inspections. Also, there is no patient labeling for this device.

Device description

Spectranetics' Excimer Laser Angioplasty (ELA) catheters consist of a bundle of optical glass fibers arranged around a guidewire lumen. Three types of ELA catheters have been evaluated in the LACI trial: Extreme Over-the-Wire (OTW), Vitesse Rapid Exchange (Rx), and Vitesse Eccentric (Vitesse-E) models. All models consist of a proximal end that which couples exclusively with the Spectranetics CVX-300 Excimer Laser. The CVX-300 Laser System is controlled by software that instructs the laser to deliver the correct energy for each catheter model. In OTW models, a bifurcation at the juncture of the proximal and distal catheter portions permits insertion of an appropriately sized quidewire (between 0.014" and 0.035" diameter) through the lumen of the catheter. In Rx models, the guidewire lumen begins 9 cm from the distal tip, to facilitate speedier removal of the laser catheter. Vitesse-E models are equipped with a torque handle to control rotation of the distal catheter tip through a 360°arc around the eccentrically positioned guidewire lumen. The ELA catheters conduct 308 nm, pulsed laser light, from the CVX 300 source to the atherosclerotic lesion or thrombus within an artery. The ultraviolet pulses ablate and debulk the lesion as the catheter tip is slowly advanced through the blockage.

Clinical study history and design

The company refers to its IDE study as the LACI (Laser Angioplasty for Critical limb Ischemia) trial. The IDE was conditionally approved as a feasibility study on December 22, 1998. The initial feasibility study (LACI l) was completed using the device for treatment of ischemic gangrene in 25 limbs of 23 patients.

An expansion of the study to a total of 192 patients (including the 25 approved for the feasibility study) and 20 sites (both US & OUS) was conditionally approved on January 26, 2001. Of the 167 patients allotted for phase 2, 30 were reserved for training (though not all of these were used). FDA's conditional approval letter for the pivotal trial included several comments and recommendations: A risk-benefit analysis would be needed for the PMA, and should include an analysis of all device- and procedure-related adverse events; the risk-benefit analysis should also quantify the purported benefits of the device (e.g., reducing stent use and/or the creation of surgical options); and it would be necessary to show that stenting (which was to be discouraged) does not confound the analysis of the study endpoints.

There are several challenges associated with the design and analysis of the LACI II trial conducted by Spectranetics. This pivotal trial is a non-randomized study, relying on a published study as an historical control. The control is the group of 673 control patients on whom 6-month follow-up was reported in: *ICAI Study Group. Prostanoids for Chronic Critical Leg Ischemia: A randomized, controlled, open-label trial with Prostaglandin E1. Ann Intern Med 1999; 130:412-421.* Of the 673 control group patients, 7 patients (1%) were

lost to follow-up, leaving 666 patients as the most appropriate denominator for some outcome variables (see statistical review memo). In the LACI II trial, 155 limbs in 145 patients were treated. Eleven LACI patients (8%) were lost to follow-up during the 6-month follow-up period, leaving 134 patients as the most appropriate denominator for some outcome variables (see statistical review memo). Note: The control study report makes no distinction between *patients* and *limbs* treated.

Laser catheter usage in the clinical trial

The following table lists the laser catheter models (and the number) used in the LACI study. It is noted that four of the models were each used only once out of 203 uses in the study.

Model #	Model description	Number used
110-001	0.9 mm Extreme	16
110-002	0.9 mm Extreme	1
110-003	0.9 mm Vitesse	5
114-001	1.4 mm Extreme	1
114-009	1.4 mm Vitesse COS	24
117-007	1.7 mm Vitesse C	1
117-016	1.7 mm Vitesse COS	22
120-001	2.0 mm Extreme	10
120-008	2.0 mm Vitesse E	10
120-009	2.0 mm Vitesse COS	17
220-006	2.0 mm Extreme II	4
222-005	2.2 mm Extreme	54
223-001	2.3 mm Extreme II	1
225-004	2.5 mm Extreme	34
225-010	2.5 mm Extreme II	3
	Total:	203

PMA Chronology

The following table provides a chronology of formal interactions for this PMA. Additional informal (e.g., e-mail, telephone) interactions, including requests for and receipt of clarification and information, occurred throughout the review process and are not outlined here.

PMA Chronology for P910001/S22

Date	**Event**
January 22, 2003	PMA received with clinical data
January 22, 2003	PMA filing date
February 14, 2003	Amendment 1: Response to request for draft SSED
March 26, 2003	Amendment 2: Response to requests for additional information, including Operator's Manual, clinical protocol, and results stratified by study center.
April 9, 2003	Amendment 3: Response to questions concerning risk-benefit

	analysis, laser parameters, and catheter recognition by system.
May 6, 2003	Major deficiency letter issued on risk analysis, safety and effectiveness results, clinical protocol, and device software and instructions for use
May 13, 2003	Meeting with applicant to discuss May 6, 2003 letter.
June 10, 2003	Amendment 5: Reply to major deficiency letter.
October 2, 2003	Scheduled for review by Circulatory System Devices Panel

Review summary

Non-clinical

The review of the biocompatibility, *in vivo* animal studies, manufacturing and sterilization information (including packaging and shelf-life) have been completed and there are no outstanding issues regarding these parts of the PMA.

Additional information was requested and received regarding the *in vitro* data provided, with respect to laser parameters, catheter recognition by system, results of shelf-life testing. The sponsor has replied to all requests for additional information.

Clinical

The sponsor was asked to address concerns raised regarding the clinical information provided in the PMA, most notably related to the following issues:

- ?? risk/benefit analysis in light of deaths, serious adverse events (including re-interventions), and persistence of CLI in the LACI population;
- ?? a discrepancy in the reported risk of major amputation;
- ?? consequences and outcomes of cases in which a perforation occurred;
- ?? reporting of event rates for the historical control group;
- ?? the number of LACI cases that met the criterion of high risk for surgical mortality, evidenced by ASA Physical Class 4 or higher;
- ?? reporting of results for the secondary Peripheral Vascular Endpoint (rate of amputation or persistent critical limb ischemia in patients surviving to 6 months);
- ?? failed guidewire crossing and use of the step-by-step laser technique;
- ?? the use of adjunctive drug therapy in the LACI study population; and
- ?? the definition for establishment of straight line flow.

All clarification and additional information requested during the review of the clinical data have been provided. The lead clinical and statistical reviews of this PMA are attached.

Summary

All FDA requests for additional information have been satisfied. The questions identified for the panel outline the issues identified as requiring discussion by the review team.